REMARKS

Status Summary

The response filed on January 12, 2006, was entered. Claims 56-60 and 62-74 are pending. Claims 56-60 and 62-74 remain rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,776,456 to Anderson et al. (Anderson) in view of U.S. 6,042,826 to Caligiuri et al. (Caligiuri), and further in view of DeAngelis (1998) *J Neurooncology* 38:245-252 (DeAngelis). Claims 56-60 and 62-74 are also rejected based on non-statutory obviousness-type double patenting as allegedly unpatentable over claim 1 in U.S. Patent No. 5,776,456 to Anderson et al. (Anderson). Reconsideration in view of the following remarks is respectfully requested.

Request for Interview with the Examiner

Given the prolonged prosecution of this application, with rejections based upon the same references, applicant respectfully requests an interview with the examiner to discuss the arguments presented herein.

Rejection of Claims Under 35 U.S.C. § 103(a)

Claims 56-60 and 62-74 remain rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,776,456 to Anderson et al. in view of U.S. 6,042,826 to Caligiuri et al., and further in view of DeAngelis (1998) *J. Neurooncology* 38:245-252. The examiner's rejection with respect to claims 56-60 and 62-67 simply references the reasons set forth in the previously issued final official action and subsequent advisory action. The examiner states that previously filed arguments and the declaration by Dr. Ellen Garber have not been found persuasive. Official action, pages 3-5.

Anderson describes methods for treatment of B cell lymphoma via administration of anti-CD20 antibodies. The examiner has previously noted that Anderson does not teach treatment of CNS lymphomas, as now claimed. The examiner concludes that it would have been *prima facie* obvious to modify the methods of Anderson to "include B-cell lymphomas of the central nervous system because such lymphomas merely represent species of the broadly claimed genus of B-cell lymphomas." First official action (paper no. 7), pages 10-12.

The examiner relies on Caligiuri as teaching that primary CNS lymphomas involve the meninges, and on DeAngelis as teaching that lymphomas are a common cause of leptomeningeal metastases. Based thereon, the examiner concludes that one of ordinary skill

in the art would reasonably expect that a subpopulation of patients with CNS lymphoma would also exhibit leptomeningeal lymphoma. Final official action (paper no. 20040722, pages 3-5. The examiner also relies on Caligiuri and DeAngelis as teaching combination of immunotherapy with chemotherapy, as in claims 4, 53, and 58. Final official action, (paper no. 20040722) pages 4-5, bridging paragraph.

The examiner bears the burden of presenting a *prima facie* case for obviousness, which requires: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) the teaching or suggestion of all the claim limitations of the applicant's invention in the combined prior art references; and (3) a reasonable expectation of success. MPEP § 2143. *See also In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). *See also, Ex parte Clapp,* 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). That is, at the time of the invention, one skilled in the art must believe that the claimed methods could be practiced with a reasonable expectation of success. Here applicant contends that, after a review of the cited references, one skilled in the art would not reasonably believe that the presently claimed methods could be practiced with an expectation of achieving therapeutic efficacy. Thus, applicant submits that the examiner has failed to meet the mandated burden.

In the official action mailed April 10, 2006, the examiner states that "the predictive value (or reasonable expectation of success) associated with the treatment of CNS lymphomas with therapeutic antibodies was specifically taught by U.S. Patent No. 6,042,826 (Caligiuri et al.)." In addition, the examiner states that he is unpersuaded by the declaration under 37 CFR 1.132 by Ellen Garber, Ph.D., in that (1) it is unclear whether the limited activity of immune effector cells in the CNS was known as of the filing date of the instant application; (2) the mechanism of cell killing by ADCC via the claimed anti-CD20 antibody was not fully appreciated until after the filing date of the instant application; (3) natural killer cells that facilitate ADCC mechanisms are present in the CNS; and/or (4) both anti-Fas and anti-CD20 antibodies can induce direct cell death via apoptosis. Each of the foregoing contentions is respectfully traversed based upon the following.

I. Caligiuri Fails to Teach Treatment of CNS Lymphomas Using Anti-CD20 Antibodies

Contrary to the assertions of the examiner, at the time of filing the instant application, a skilled artisan would not believe that there was a reasonable chance of success in practicing

the claimed invention. Applicant further discusses the previously filed declaration pursuant to 37 C.F.R. § 1.132 by Ellen Garber, Ph.D. As stated therein, the cited documents are not reasonably predictive of the success of anti-CD20 therapy for the treatment of CNS lymphomas, notwithstanding the success of systemic anti-CD20 therapy. In particular, the examiner's analysis focuses on the mechanics of intrathecal antibody administration without considering the biological basis of particular treatments.

Applicant strongly contests the examiner's conclusion that treatment of CNS lymphomas by intrathecal administration of anti-Fas antibodies, as described in the Caligiuri patent, is relevant to the potential therapeutic efficacy of anti-CD20 antibodies for treating CNS lymphomas. Applicant acknowledges that Caligiuri describes intrathecal antibody administration, however, any efficacy of anti-Fas antibodies is not at all relevant to the therapeutic efficacy of anti-CD20 antibodies. As detailed below, a skilled artisan would not conclude that the efficacy of intrathecally administered anti-CD20 antibodies could be reasonably predicted based upon the use of anti-Fas antibodies given that anti-Fas antibodies and anti-CD20 antibodies (a) recognize distinct antigens having unique expression profiles, and (b) confer therapeutic effects by entirely different modes of action. *See* Declaration by Ellen Garber, Ph.D., ¶¶ 17-36 (of record).

The Caligiuri patent describes treatment of primary central nervous system lymphoma (PCNSL) using a Fas-cross-linking composition to elicit Fas-mediated cytotoxicity. The Caligiuri patent states that the Fas-cross-linking composition can be an anti-Fas antibody having agonist activity or soluble Fas ligand. Fas, also called APO-1 or CD95, is a transmembrane receptor that is a member of the tumor necrosis factor (TNF) receptor family, which trigger apoptosis by activating a cascade of specific proteases called caspases. The activated caspases cleave cellular components, a process that leads to morphological cellular and nuclear changes as well as to degradation of chromosomal DNA.

Initially, applicant submits that any therapeutic success obtained in targeting Fas antigen is not predictive of potential therapeutic success in targeting the CD20 antigen, even if both antigens are expressed on malignant cells of the same lineage. The inability to extrapolate the suitability of one antigen target for another stems from differences in antigen expression profiles, including antigen localization (*i.e.*, intracellular or membranous, or a combination thereof), antigen density, antigen expression levels, antigen expression on malignant cells as compared to normal cells, antigen expression on subpopulations of malignant cells, antigen expression at particular times of the cell cycle, antigen half-life,

antigen glycosylation and other post translational modifications that affect antigen accessibility, stability / strength of binding to an antibody, and antigen internalization upon antibody binding. These differences were noted in the response filed January 12, 2006, and are presented again herein because the examiner has not considered these arguments. Based thereon, Caligiuri is relevant only for the teaching that antibodies can be administered intrathecally, *i.e.*, the mechanics of administration, but do not bear on the expectation of successfully treating CNS lymphomas using anti-CD20 antibodies.

In addition to targeting of different antigens, anti-Fas and anti-CD20 antibodies operate via different modes of action. More specifically, in contrast to the agonistic anti-Fas antibodies described in Caligiuri, the therapeutic efficacy of anti-CD20 antibodies primarily relies on induction of antibody-dependent cell-mediated cytotoxicity (ADCC) and cell dependent cytotoxicity (CDC), which each involve immune system effector cells, *i.e.*, NK cells and macrophages, to effect lysis of antibody-targeted cells. *See* Declaration by Ellen Garber, Ph.D., ¶¶ 22-30. The therapeutic efficacy of anti-CD20 antibodies, which requires recruitment of immune cells, is different from that of anti-Fas antibodies, which relies on direct induction of apoptotic changes within tumor cells (*i.e.*, without the action of lymphoid and myeloid effector cells).

DeAngelis is not discussed further as the examiner states that his reliance on this reference as a secondary teaching of inclusion of known chemotherapeutics (*i.e.*, methorexate and ^{111}In-diethylenetriamine) when treating neoplasms of the brain and not to support predictive value of treating brain disorders. Official action, page 4. Based upon the examiner's explanation, it is understood that this reference is cited only against dependent claim 58, which specifies the additional administration of cytarabine and thiotepa or methotrexate and ^{111}In-diethylenetriamine pentaacetic acid.

II. At the Time of the Instant Invention, Immunological Privilege of the CNS Was Known

Immunological privilege refers to the lack of or reduced capacity of particular tissues to mount an immune response. Both active and passive mechanisms are believed to establish immunological privilege, including antigen sequestration, maintenance of an immunosuppressive local environment, physical blockade of immune cells via the blood-brain barrier, and induction of apoptotic death in infiltrating cells of the immune system.

Applicant has previously presented arguments that the success of anti-CD20 antibodies for the treatment of CNS lymphomas was unexpected in part because anti-CD20

antibodies rely on immune effector cells, whose activity is limited in the CNS. In support of the declaration by Dr. Ellen Garber, a journal publication by Friese et al. (Friese) was submitted with the response filed January 12, 2006, which states:

> The central nervous system (CNS) participates in responses of the innate immune system. However, immune inhibitory and anti-inflammatory mechanisms physiologically outbalance and counteract immune activity and thereby limit immune-mediated tissue damage in brain. Human gliomas appear to take advantage of this immunosuppressive milieu.

In considering this reference, the examiner notes that it was published four years after the filing date of the instant application, and concludes that it is unclear if the assumption of non-enablement would have been relevant at the time of filing. Official action, page 5. In response, applicant clarifies that the CNS has long been recognized as immunoprivileged, which is reiterated in the recent publication of Friese. A journal article by Pollack et al. (Pollack, copy enclosed), which was published at about the time of the priority date of the instant application, similarly summarizes the uncertainty in treating brain tumors. The authors explain that immunotherapies have failed to yield consistently promising results in initial trials as a result of unique immunobiological features of the CNS, including:

> (1) the presence of a blood-brain barrier that, although partially disrupted by the tumor, functions to exclude elements of the immune system from the tumor or brain parenchyma; (2) a lack of organized secondary lymphatic tissues supporting efficient immune responses locally in the CNS; (3) low levels of expression of major histocompatibility complex proteins in the CNS; (4) an apparent paucity of the most efficient antigen-presenting cells; and (5) glioma-derived immunosuppressive factors, such as transforming growth factor-beta, that interfere with the induction of local as well as systemic immune responses to the tumor.

As evidenced by Pollack, at the time of the instant invention, it was unknown whether the central nervous system could initiate effective cell-mediated immune responses such as ADCC and CDC. Therefore, a skilled artisan could not reasonably predict that anti-CD20 antibodies, which rely on ADCC and CDC, could be used as an effective therapy for the treatment of CNS lymphomas.

The examiner further states that Friese clearly teaches that natural killer cells, which mediate ADCC, are present in the CNS. Official action, page 5. This observation does not negate the establishment of immunological privilege by immune inhibitory mechanisms described in both Friese and Pollack.

III. At the Time of the Instant Invention, Induction of ADCC by Anti-CD20 Antibodies Was Known

With further reference to the state of the art as of the filing date of the instant application, the examiner states that "it would appear that the mechanism of cell killing by ADCC via the claimed anti-CD20 antibodies was not fully appreciate until after the filing date of the instant application . . . ." Official action, page 5. Applicant responds that, at the time of the instant invention, induction of ADCC by anti-CD20 antibodies was known in the art. In particular, U.S. Patent No. 5,776,456 to Anderson et al. describes that immunologically active anti-CD20 antibodies bind human Clq, mediate complement dependent lysis ("CDC") of human B lymphoid cell lines, and lyse human target cells through antibody dependent cellular cytotoxicity ("ADCC"). *See* e.g., col. 7, lines 16-22. Accordingly, that anti-CD20 antibodies induced cell-mediated immune responses was known at the time of the instant invention. Thus, when considering the mechanism of anti-CD20 antibodies, and the immunological privilege of the CNS, a skilled artisan would not reasonably conclude that anti-CD20 antibodies could be effective for the treatment of CNS disorders.

In considering the different modes of action between the anti-Fas antibodies of Caligiuri and the anti-CD20 antibodies of the instant invention, the examiner dismisses the above-noted requirement for immune effector cells, stating that anti-CD20 antibodies can also direct cell death via apoptosis. Official action, page 5, citing declaration by Ellen Garber, Ph.D. Applicant acknowledges that induction of apoptosis is an additional therapeutic mechanism of anti-CD20 antibodies. However, as also stated in the Declaration by Ellen Garber, Ph.D., ¶¶ 33-34, apoptosis of CD20-expressing cells requires the presence of secondary IgG antibodies or FcR-expressing cells. This requirement for additional FcR-expressing cells was known as of the priority date of the instant application. *See e.g.*, Shan et al. (1998) *Blood* 91(5)): 1644-1652 (of record) and Shan et al. (2000) *Cancer Immunol. Immunother.* 48(12): 673-683 (of record). Therefore, in contrast to the mechanism of action of classic chemotherapeutic drugs and anti-Fas antibodies, which directly induce apoptotic changes within tumor cells (*i.e.*, without the action of lymphoid and myeloid effector cells), the cytotoxicity of anti-CD20 antibodies depends on the recruitment of immune system effector cells, particularly FcR-expressing NK cells and macrophages, whose activity in the CNS was uncertain.

Based upon the differences in the mode of action of anti-Fas antibodies and anti-CD20 antibodies, which were known at the time of the instant invention, the use of anti-CD20 antibodies for the treatment of CNS lymphomas was unpredictable notwithstanding the success of intravenously administered systemic rituximab for non-CNS lymphomas or therapies employing apoptotic inducing antibodies such as anti-Fas antibodies. *See* Declaration by Ellen Garber, Ph.D., ¶¶ 35-36.

Based on the foregoing, one skilled in the art would not be motivated to replace the anti-Fas antibody in the methods of Caligiuri with an anti-CD20 antibody of Anderson to arrive at the presently claimed invention. In the absence of a motivation to practice the claimed invention based on a reasonable chance of success, the claims are not *prima facie* obvious. Accordingly, applicant respectfully requests that the rejection of claims 56-60 and 62-74 under 35 U.S.C. § 103(a) based on Anderson, Caligiuri, and DeAngelis be withdrawn.

Rejection of Claims Based on Non-Statutory Obviousness-Type Double Patenting

Claims 56-60 and 62-74 remain rejected based on non-statutory obviousness-type double patenting as allegedly unpatentable over claim 1 in U.S. Patent No. 5,776,456. The examiner's basis for rejection is the same as that set forth above with respect to 35 U.S.C. § 103(a). Official action, pages 5-6. This rejection is respectfully traversed.

Based on the arguments set forth above in response to the rejection of claims under 35 U.S.C. § 103(a), which are incorporated herein, applicant believes that the methods of the present disclosure are non-obvious in view of Anderson. As such, applicant also requests that the obviousness-type double patenting rejection be withdrawn.

Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

PILLSBURY WINTHROP SHAW PITTMAN LLP

/Julie Broadus Meigs/

Julie Broadus Meigs Ph.D.
Registration No. 47,447

P.O. Box 10500
McLean, VA 22102
(703) 770-7772 Direct Dial
(703) 770-7901 Facsimile

Date: July 10, 2006